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### (54) Title: NUCLEOSIDE DERIVATIVES AS INHIBITORS OF RNA-DEPENDENT RNA VIRAL POLYMERASE

(57) Abstract: The present invention provides nucleoside compounds and certain derivatives thereof which are inhibitors of RNA-dependent RNA viral polymerase. These compounds are inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection. They are particularly useful as inhibitors of hepatitis C virus (HCV) NS5B polymerase, as inhibitors of HCV replication, and/or for the treatment of hepatitis C infection. The invention also describes pharmaceutical compositions containing such nucleoside compounds alone or in combination with other agents active against RNA-dependent RNA viral infection, in particular HCV infection. Also disclosed are methods of inhibiting RNA-dependent RNA polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection with the nucleoside compounds of the present invention.

# INTERNATIONAL SEARCH REPORT

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) HCA Plus structure search			
C. DOCUMENTS CONSIDERED TO BE RELEVANT			
Category *	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
A	DATABASE HCAPLUS, Chemical Abstracts, Vol Abstract No. 365176, HCA Plus Accession Number USA), WO 03/093290 A2 (GENELABS TECHNO HCA Plus Abstract supplied, see pages 3-4 of abstract	er 2003:892793 (Columbus, Ohio, LOGIES, INC.) 13 November 2003,	1-16
X, P	WO 02/057287 A2 (MERCK & CO., INC.) 25 July 2002, see entire document.		1-16
X, P	WO 02/057425 A2 (MERCK & CO., INC.) 25 July 2002, see entire document.		1-16
х	WO 01/16379 A1 (MERCK & CO., INC.) 08 March 2001, see entire document.		1-16
х	LI ET AL. 2'-C-Branched Ribonucleotides. 2. Synthesis of 2'-C-beta-Trifluoromethyl Pyrimidine Ribonucleosides. Organic Letters. 08 March 2001, Vol. 3, Issue No. 7, pages 1025-1028, see entire document.		1, 7
х	DUNKEL ET AL. Synthesis of 2'-C-Difluoromet Ribonucleoside Replacements in Hammerhead Ribo 1995, Vol. 14, Issue Nos. 3-5, pages 799-801, see	ozymes. Nucleosides & Nucleotides.	1-3, 7
		See patent family annex.	
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